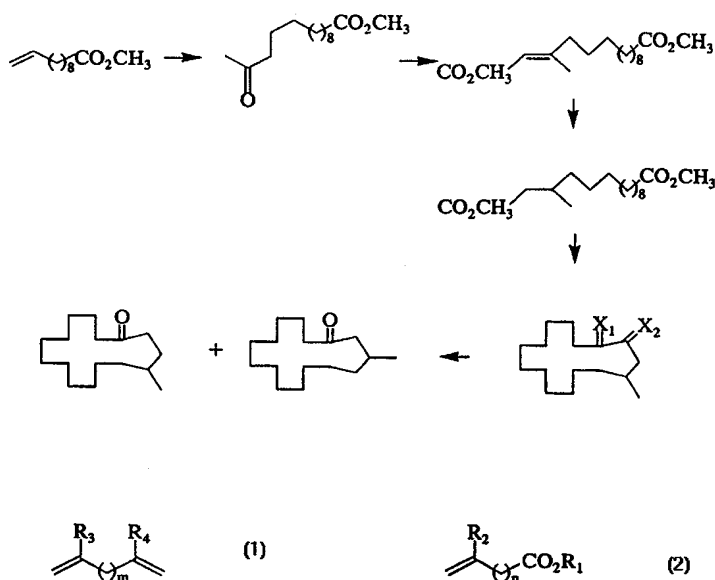




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(54) Title: PREPARATION OF MACROCYCLIC KETONES UTILISING ADDITION OF KETONES TO ALKENES



(57) Abstract

The invention provides a process for the preparation of macrocyclic ketones by a reaction sequence wherein one step is the radical addition of ketone to alkene of the form (1), where $\text{R}_3 = \text{H}$ or lower alkyl, $\text{R}_4 = \text{H}$ or lower alkyl, $m = 4$ to 8, or form (2), where $\text{R}_1 = \text{alkyl}$, $\text{R}_2 = \text{H}$ or alkyl, $n = 4$ to 8. The process can be used to produce macrocyclic ketone mixtures, particularly those containing muscone which are useful in producing fragranced products.

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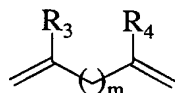
Preparation of macrocyclic ketones utilising addition of ketones to alkenes

Field of the Invention

- 5 This invention concerns the preparation of macrocyclic ketones by a reaction sequence wherein one step in the sequence is the addition of a ketone to an alkene.

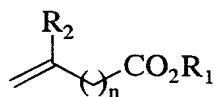
Summary of the Invention

- 10 In one aspect the invention provides a process for the preparation of macrocyclic ketones by a reaction sequence wherein one step in the sequence is the radical addition of ketone to alkene and wherein said alkene is selected from alkenes having the formula :



- 15 where $\text{R}_3 = \text{H}$ or lower alkyl
 $\text{R}_4 = \text{H}$ or lower alkyl
 $m = 4$ to 8 .

or



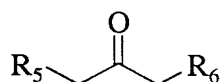
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- where $\text{R}_1 =$ alkyl
 $\text{R}_2 =$ H or alkyl
 $n = 4$ to 8

R_1 and R_2 are preferably lower alkyl groups.

The term "lower alkyl" is used in this specification to mean an alkyl group having from 1 to 4 carbon atoms.

The ketone has the general formula:

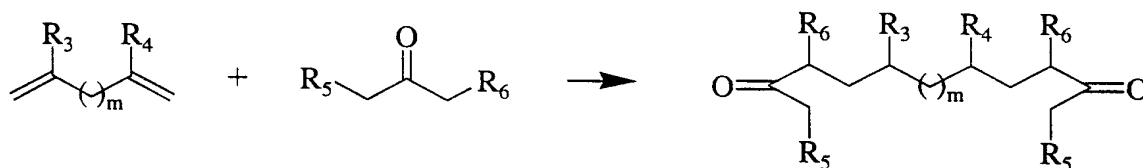


where $\text{R}_5 = \text{H or lower alkyl}$

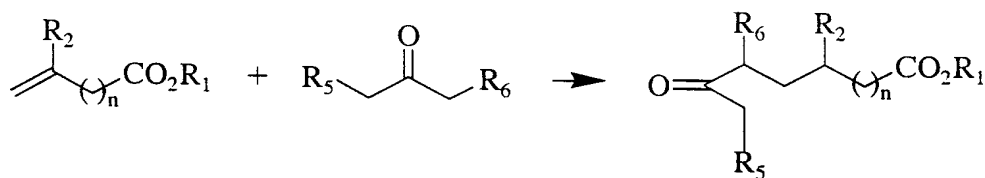
$\text{R}_6 = \text{H or lower alkyl}$

Suitable ketones include, for example, acetone, 2-butanone, 3-pentanone etc.

The addition reaction is as follows:



or



Initiation of the addition reaction is preferably carried out by *in situ* generation of manganese (III) from manganese (II) by redox reaction, e.g. mediated by potassium permanganate, as this gives good chemoselectivity (see T. Linker *et al.*, *Tetrahedron*, **51**, 9917, (1995)). Manganese (III) may alternatively be generated *in situ* from manganese (II) by anodic oxidation (e.g. as described in I. Nishiguchi *et al.*, *Tetrahedron*, **47**, 831 (1991) and R. Warsinsky, E. Steckhan, *J. Chem. Soc. Perkin 1*, 2027, (1994)). A further

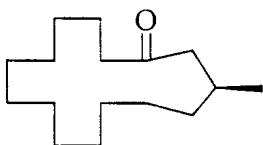
possibility is direct use of manganese (III) acetate, although this is less favoured because of difficulties of preventing over-oxidation of the intermediate radical educts.

Alkene starting materials can be obtained commercially or can be synthesised, e.g. by Wittig reaction.

The final products of the process of the invention are macrocyclic ketones, such as muscone, with useful fragrance properties. The reaction products of the addition of ketone to alkene must be capable of forming a macrocyclic ketone, and, therefore, there need to be sufficient carbon atoms between the two keto-functionalities or the keto- and ester functionalities (depending upon the starting alkene) of these intermediate products. For these reasons it is preferred to use alkenes in which $m = 6$ to 8 or in which $n = 6$ to 8 , particularly $n = 8$ (i.e. undecylenic acid esters).

If the ultimate product has too high a molecular weight (e.g. being produced from a long chain ester and a larger ketone) it will be outside the range of olfaction. Smaller ketones, particularly acetone and 2-butanone, are therefore generally favoured as reactants.

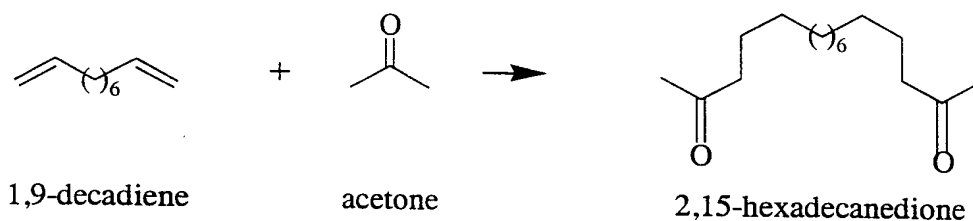
Muscone is the common name of (-)-3-methylcyclopentadecanone which has the following structure:



Muscone is the principal odorous constituent of the musk deer gland, and is a useful fragrance material. Since elucidation of its structure in 1926 (see Ruzicka, L., *Helv. Chim. Acta*, **9**, 230 (1926)), many syntheses both of the optically-active material and racemic muscone have been reported. These syntheses, while elegant, generally involve many stages and may require expensive and/or inaccessible starting materials. Hitherto

there has thus been no short and efficient method of producing muscone which utilises inexpensive and readily accessible starting materials.

In accordance with the invention, reaction of 1,9-decadiene ($R_3 = H$, $R_4 = H$, $m = 6$) with
 5 acetone gives 2,15-hexadecanedione, as follows:

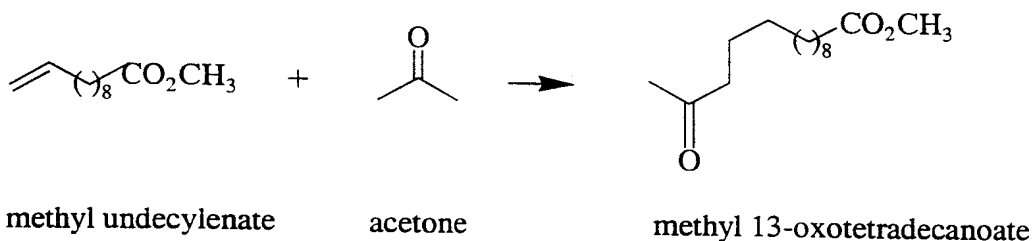


1,9-decadiene may be prepared in known manner, e.g. by ethenylation of cyclooctene (Szmant, H.H., '*Organic Building Blocks of the Chemical Industry*', Wiley Interscience, New York, p310 (1989)).

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The resulting 2,15 hexadecanedione may be converted to muscone, e.g. in various known ways including by intramolecular aldol reaction (Stoll, M., Rouve, A. *Helv. Chim. Acta*, **30**, 2019, (1947), Tsuji, J., *et al.*, *Tet. Lett.*, 2257 (1979), Tsuji, J., *et al.*, *Bull. Chem. Soc. Jpn.*, 1417, **53** (1980) and Sakurai, H., *et al.*, *J. Organomet. Chem.*, **264**, 229, (1984)),
 15 followed by hydrogenation (see Figure 2). A further approach is high temperature cyclisation over a suitable catalyst, as described in EP 400509 of BASF.

Alternatively, reaction of methyl undecylenate ($R_1 = CH_3$, $R_2 = H$, $n = 8$) (or other ester of undecylenic acid) with acetone produces methyl 13-oxotetradecanoate, as follows:



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The resulting methyl 13-oxotetradecanoate can then be converted, e.g. using known techniques, to muscone. For example, in a subsequent 4 step conversion, Wittig-Horner (or Wadsworth-Emmons) reaction of methyl 13-oxotetradecanoate with trimethyl phosphonoacetate gives 3-methylpentadec-2-endioic acid dimethyl ester. Reduction of this material, by catalytic hydrogenation, gives dimethyl 3-methylpentadecanedioate. Cyclisation of this material, e.g. on treatment with sodium in refluxing xylene, under nitrogen, gives a mixture of acyloins, 2-hydroxy-4-methyl-1-cyclopentadecanone and 2-hydroxy-14-methyl-1-cyclopentadecanone, which are not readily separable. Heating the mixture of acyloins with zinc and hydrochloric acid produces a mixture of muscone and 4-methylcyclopentadecanone. This series of reactions is illustrated in Figure 1. Muscone can be separated from the resulting mixture, e.g. by silica gel chromatography. However, the mixture has good olfactive properties and can be used as a fragrance or perfume ingredient.

The macrocyclic ketones which are the products of the process of the invention may be produced separately or in the form of mixtures. Both separate ketones and mixtures may have fragrance properties that render the materials suitable for perfumery use in known manner.

The invention also covers macrocyclic ketones which are the direct product of the method of the invention, in particular mixtures of muscone, with 4-methylcyclopentadecanone, produced directly by the method of the invention. Such mixtures normally contain other components that are an incidental product of the reaction and mixtures which are the direct product of the process of the invention without further purification are a further aspect of the invention. Alternatively, substantially pure macrocyclic ketones can be isolated by further purification of the reaction product by conventional means such as chromatography or fractional distillation.

The macrocyclic ketones may be used as ingredients of perfumes (or fragrance compositions) and perfumed products in known manner, e.g. as described in WO 98/09933, and the use of the direct products of the process of the invention, comprising

mixtures containing macrocyclic ketones is a further aspect the invention. A perfume or perfumed product according to this aspect of the invention comprises a mixture containing macrocyclic ketone, particularly muscone, produced by the method of the invention, in an olfactively effective amount.

5

A "perfume" or "fragrance composition", as used herein, means a composition comprising various fragrance materials, and optionally a solvent, formulated to have certain useful fragrance characteristics. In most cases fragrance compositions are formulated to have a fragrance generally considered at least inoffensive and, preferably, pleasing to intended users of the composition. Fragrance compositions are used for imparting a desired odour to the skin and/or any product for which an agreeable odour is indispensable or desirable. Examples of such products are personal and household products including fabric washing powders, washing liquids, fabric softeners and other fabric care products; detergents and household cleaning, scouring and disinfection products; air fresheners, room sprays and pomanders; fine fragrances; soaps, bath and shower gels, shampoos, hair conditioners and other personal cleansing products; cosmetics such as creams, ointments, toilet waters, preshave, aftershave, skin and other lotions, talcum powders, body deodorants and antiperspirants etc. Fragrance compositions are also used in products that would normally have an unattractive or offensive odour to mask this odour and produce an odour that is less unattractive or offensive. Products in this category include fuel odorants. The (generally pleasing) fragrance characteristics may be the main function of the product in to which the fragrance composition has been incorporated, as in the case of fine fragrances, or may be ancillary to the main function of the product, as, e.g., in the case of detergents, cleaning products and skin care products.

In perfumes an amount of 0.01% by weight or more of a macrocyclic ketone produced according to the invention will generally have a clearly perceptible olfactive effect. Preferably the amount is in the range 0.1 to 80% by weight, more preferably at least 1%. The amount of the ketone produced according to the invention present in products will generally be at least 10 ppm by weight, preferably at least 100 ppm, more preferably at least 1000 ppm. However, levels of up to about 20% by weight may be used in particular cases, depending on the product to be perfumed.

The invention will be further described, by way of illustration, in the following Examples and with reference to the accompanying Figures, in which:

Figure 1 shows the reaction scheme for radical addition of acetone to methyl undecylenate to produce methyl 13-oxotetradecanoate, and subsequent reaction of this to produce a mixture of muscone and 4-methylcyclopentadecanone; and

Figure 2 shows the reaction scheme for radical addition of acetone to 1,9-decadiene to produce 2,15-hexadecanedione, and subsequent reaction of this to produce muscone.

Example 1

This concerns radical addition of acetone to methyl undecylenate to produce methyl 13-oxotetradecanoate, and subsequent reaction of this to produce a mixture of muscone and 4-methylcyclopentadecanone. The reaction scheme is shown in Figure 1.

Synthesis of Methyl 13-oxotetradecanoate

A mixture of potassium acetate (70 g; 720 mmol), manganese (II) acetate tetrahydrate (1g; 0.4 mmol), acetone (300 ml) and glacial acetic acid (200ml) was heated at 70° C under N₂. Methyl undecylenate (39 g; 0.21 mol) was then added, followed by the addition of solid potassium permanganate (12.6 g; 0.8 equivalents), which was added in very small portions at 70° C over a period of 4 hours.

The reaction mixture was cooled to room temperature, diluted with water (1.5 l) and extracted into dichloromethane (2 x 500 ml). The combined organic extracts were washed with saturated NaHCO₃ (aq), then water, and finally dried over anhydrous MgSO₄. The solvent was removed *in vacuo* to give a pale yellow oil (56.0 g). glc [SE 54; 100-250° C @ 4° C min⁻¹] indicated a high degree of conversion.

<u>methyl undecylenate</u>	<u>crude produced</u>
12.354 min 99.1%	25.680 min (81.5%)

The crude product was vacuum distilled, giving a pale yellow oil which solidified 20.9 g, 39%. Glc (as above) indicated 92% purity.

5 ¹³C NMR (CDCl₃) 23.7514(CH₂), 24.8371(CH₂), 29.0197(CH₂), 29.0579(CH₂),
29.1191(CH₂), 29.2643(CH₂), 29.2796(CH₂),
29.3026(CH₂), 29.3790(CH₂), 29.7002(CH₃), 34.1146(CH₂),
43.8177(CH₂), 52.4324(OCH₃), 174.1612(C=O, ester),
209.1505(C=O).

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Synthesis of Dimethyl 3-Methyl-2-pentadecanedioate

A Wittig-Horner (or Wadsworth-Emmons) reaction was followed by catalytic hydrogenation.

15

Trimethyl phosphonoacetate (82 g; 0.45 mol) was added dropwise with stirring to a suspension of oil-free sodium hydride (12 g; 0.5 mol) in tetrahydrofuran (THF) (300 ml). After 1 hour, methyl 13-oxotetradecanoate, [102.4 g; 0.4 mol], dissolved in THF (150 ml) was added dropwise, and the reaction mixture refluxed, with stirring, under nitrogen for 3 hours. After cooling, the reaction mixture was poured into water and extracted into diethyl ether. The combined ether extracts were washed, and dried over MgSO₄.

20

Glc [SE54: 100-250° C @ 4° C min⁻¹] indicated a 90% conversion.

The solvent was removed *in vacuo* and the residue was vacuum distilled, using a Vigreux column to give dimethyl (E-, Z-)-3-methyl-2-pentadecenedioate as a colourless oil (114.3g; 91.6%), bp 170° C at 0.15 mbar.

25

This product was dissolved in methanol (400 ml) and 5% palladium on carbon (5 g) was added. The reaction mixture was hydrogenated in a 1 litre Buchi autoclave at 5 bar H₂ pressure for 7 hours. Glc (as above) now showed one major peak (90.4%). The catalyst

30

was removed by filtration through Celite and the solvent removed to give a crude product which was vacuum distilled to give dimethyl 3-methyl-2-pentadecanedioate (104.5 g).

5 Synthesis of 2-Hydroxy-4-Methyl-1-Cyclopentadecanone and 2-Hydroxy-14-Methyl-1-Cyclopentadecanone

Dimethyl 3-methyl-2-pentadecandioate (11.3 g; 0.036 mol) was dissolved in xylene (80ml) and added, over one hour, to finely-dispersed sodium microgranules (<0.1 mm
10 particle size, Acros) in xylene (500 ml). The reaction mixture was maintained under nitrogen throughout, and refluxing was continued for 30 minutes following complete addition.

The mixture was cooled, and treated, in a stream of nitrogen, with ethanol (25 ml). The
15 xylene solution was washed free of alkali, dried over MgSO_4 , then the solvent was removed *in vacuo*. The residue was short-path distilled to give a pale green oil (8.7 g; 93%) b.p. 125°C @ 0.1 mbar. glc [SE54; $100\text{--}250^\circ \text{C}$ @ $4^\circ \text{C min}^{-1}$] showed only one product peak 28.043 min 91%. ^1H and ^{13}C NMR indicated the presence of both acyloins, 2-hydroxy-4-methyl-1-cyclopentadecanone ($\text{X}_1=\text{O}$, $\text{X}_2=\text{H}$, OH in Figure 1) and
20 hydroxy-14-methyl-1-cyclopentadecanone ($\text{X}_1=\text{H}$, OH, $\text{X}_2=\text{O}$ in Figure 1).

The experiment was repeated (5x scale) in order to obtain further material for the final stage.

25 Synthesis of Muscone and 4-Methylcyclopentadecanone

The mixture of acyloin products [39.3 g; 0.155 mol] was dissolved in 1,4-dioxan (1 litre). Zinc pellets (60 g) were added, and the reaction mixture was refluxed with stirring while passing HCl(g) . After 2 hours, glc [SE54; $100\text{--}250^\circ \text{C}$ @ $4^\circ \text{C min}^{-1}$] indicated complete
30 conversion to two products.

The reaction mixture was filtered to remove excess zinc, then washed with water, followed by $\text{NaHCO}_3(\text{aq})$, then a final water wash. The solvent was removed *in vacuo*, and the crude residue was chromatographed [silica; hexane 85%, Et_2O 15%] to give a colourless oil, which was vacuum distilled using a short Vigreux side arm. This gave a colourless oil (27.3 g; 74%), being a mixture of

3-methylcyclopentadecanone (31.2%) Kovats 1870

4-methylcyclopentadecanone (65.7%) Kovats 1888

The mixture has good olfactive properties and is useful as a fragrance material as it stands.

Muscone can be separated from the mixture if desired, e.g. by silica gel chromatography.

Example 2

In a variant of Example 1, butan-2-one (2-butanone) was used in place of acetone and was added with high regioselectivity to methyl undecylenate. The product was homologated and cyclised to give a mixture of 3,4-dimethylcyclopentadecanone and 4,5-dimethylcyclopentadecanone in analogous manner to Example 1. The resulting mixture smelled musky.

Synthesis of 3,4-Dimethylcyclopentadecanone and 4,5-Dimethylcyclopentadecanone

a) Synthesis of Methyl 12-Methyl-13-oxotetradecanoate

A mixture of potassium acetate (140 g), manganese (II) acetate tetrahydrate (2.0 g), butan-2-one (500 g), and glacial acetic acid (300 ml) was heated @ 70° C under N_2 . Methyl undecylenate (80 g; 0.43 mol) was added, followed by portionwise addition of potassium permanganate (25.0 g) over 2 hours.

The reaction mixture was cooled to room temperature, water (2000 ml) was added, and the reaction mixture was extracted into diethyl ether. The organic extracts were washed thoroughly with water, then aqueous sodium bicarbonate. Removal of solvent gave a pale yellow oil, which was subjected to vacuum distillation through a Vigreux column. After a fore-run consisting of unreacted methyl undecylenate, the title material was obtained as a colourless oil (32.0 g) bp 146° C @ 0.6 mm Hg. M+270. ¹H and ¹³C NMR confirmed the structure, and indicated the absence of the isomeric methyl 13-oxopentadecanoate.

¹³C NMR (CDCl₃) 7.7732 (CH₃), 16.4670(CH₃), 24.9238(CH₂), 27.3171(CH₂), 29.0681(CH₂), 29.2210(CH₂), 29.3815(CH₂), 29.4810(CH₂), 29.6721(CH₂), 33.1435(CH₂), 34.0534(CH₂), 34.1917(CH₂), 46.0734(CH), 51.3569(OCH₃), 174.2095(C=O ester), 215.3541(C=O).

b) Synthesis of Dimethyl 3,4-Dimethylpentadecanedioate

Trimethyl phosphonoacetate (25.0 g; 0.133 mol) was added dropwise with stirring to a suspension of oil-free sodium hydride (3.6 g; 0.15 mol) in dry THF (150 ml). After complete addition, methyl 12-methyl-13-oxotetradecanoate (32.0 g; 0.12 mol) was added dropwise, and the reaction mixture was refluxed with stirring for a total of 8 hours.

Most THF was removed *in vacuo* and the residue was partitioned between diethyl ether and water. The organic layer was separated, washed with water, and dried over MgSO₄.

Chromatography on silica, using a mixture of hexane (90%) and diethyl ether (10%) as eluent gave dimethyl 3,4-dimethyl-2-pentadecenedioate (31.2 g) as a colourless oil.

This unsaturated diester (25.0 g) was dissolved in methanol (250 ml), and 5% Pd/C added. The reaction mixture was hydrogenated @ 6 bar hydrogen pressure until uptake ceased. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo* to give a colourless oil. Chromatography (conditions as above) gave a colourless

oil (23.2 g), identified as dimethyl 3,4-dimethylpentadecanedioate. Glc [SE54: 100°C-250° C @ 4° C/min] indicated 98% purity.

c) Synthesis of 3,4-Dimethylcyclopentadecanone and 4,5-Dimethylcyclopentadecanone

Dimethyl 3,4-dimethylpentadecanedioate (14.0 g; 0.042 mol) was dissolved in xylene (80ml), and added dropwise over 1 hour to a suspension of sodium (0.1 mm particle size) in xylene (80 ml). The addition was carried out under nitrogen, and the reaction mixture was refluxed for a further 30 minutes under nitrogen before cooling, and treating dropwise with ethyl alcohol (100 ml.), in a stream of nitrogen. The xylene solution was then washed free of alkali with water.

TLC [silica: hexane 80%, diethyl ether 20%] indicated the reaction to have gone to completion. The xylene solution was dried over MgSO_4 , and the solvent removed *in vacuo* to give the mixture of acyloin intermediates as a pale yellow oil (8.2 g). This was dissolved in 1,4-dioxan (250 ml), and zinc dust (15 g) added. The reaction mixture was heated to reflux and hydrogen chloride gas was passed with stirring for 1 hour. The reaction mixture was filtered through Celite, and the solvent removed from the filtrate *in vacuo* to give a colourless oil (3.8 g). This was chromatographed on silica, using hexane as eluent, gave a colourless oil (1.3 g), identified as 1,2-dimethylcyclopentadecane, obtained by over-reduction. Further elution, using a mixture of hexane (90%) and methyl *tert*-butylether (10%) as eluent, gave a colourless oil (1.1 g) identified as a mixture of 3,4-dimethylcyclopentadecanone and 4,5-dimethylcyclopentadecanone. The mixture had a musky smell.

glc[SE54 100°C-250° C @ 4° C/min]

26.052 min	33.6%	M+252
26.210 min	14.8%	M+252
26.500 min	33.1%	M+252
26.722 min	11.5%	M+252

Example 3

This concerns radical addition of acetone to 1,9-decadiene to produce 2,15-hexadecanedione. This may be subsequently reacted in known manner to produce muscone. The reaction scheme is shown in Figure 2.

Synthesis of 2,15-Hexadecanedione

A mixture of potassium acetate (70 g; 720 mmol), manganese (II) acetate tetrahydrate (1g; 0.4 mmol), acetone (300 ml) and glacial acetic acid (150 ml) was heated at 70° C under N₂. 1,9-Decadiene (35.0 g; 0.25 mol) was then added, followed by solid potassium permanganate (12.6 g; 0.8 equivalent), which was added in very small portions at 70° C over a period of 4 hours. The reaction mixture was then cooled, diluted with water (1500 ml), and extracted into dichloromethane. The combined organic extracts were washed with saturated NaHCO₃ (aq), then water, and finally dried over MgSO₄. The solvent was removed *in vacuo* to give a pale yellow oil (58.2 g). Glc [SE 54; 100-250° C @ 4° C min⁻¹] indicated 70.4% conversion.

Tlc [silica: hexane 50%, Et₂O 50%] indicated a major product, which was separated by chromatography (as Tlc), to give a colourless solid (25.2 g). This was recrystallised to give colourless crystals (18.9 g, 29%), mp 80° C (hexane).

¹³C NMR (CDCl₃): δ209.2(C=O), 43.7 (CH₂C=O), 29.8 (CH₃C=O), 29.5 (CH₂)
29.4 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 23.8 (CH₂).

The 2,15-hexadecanedione may be converted to muscone in known manner, e.g. by an internal Aldol reaction followed by hydrogenation, e.g. using 5% palladium on carbon catalyst.

A different, cheaper approach involves the high temperature cyclisation over a suitable catalyst. Such methodology is described in EP 400509 of BASF. Such catalyst methods

enable greater than 60% conversion with high selectivity, providing a short and inexpensive synthesis of racemic muscone.

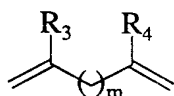
5 In a variant of Example 3, the procedure was repeated using a longer diene ($m = 8$) (synthesised by Wittig reaction) in place of 1,9-decadiene ($m = 6$). The expected product was obtained.

6. A process according to any one of claims 1 to 3, comprising reaction of 1,9-decadiene with acetone to produce 2,15-hexadecanedione.

5 7. A process according to claim 6, wherein the 2,15-hexadecanedione is converted to muscone.

8. A method of preparing a macrocyclic ketone comprising radical addition of ketone to alkene having the formula

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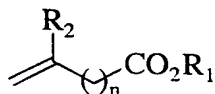
where R_3 = H or lower alkyl

R_4 = H or lower alkyl

m = 4 to 8

15 to produce a dione, followed by cyclisation of said dione by an intramolecular aldol reaction or by cyclisation over a catalyst.

9. A method of preparing a macrocyclic ketone comprising radical addition of ketone to alkene having the formula



20

where R_1 = alkyl

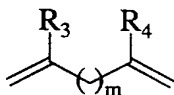
R_2 = H or alkyl

n = 4 to 8

to form a ketoester followed by reaction of the ketoester with trimethylphosphonoacetate,
25 reduction of the resultant product, cyclisation to an acyloin and reduction of the acyloin.

17

10. Radical addition of ketone to alkene wherein said alkene is selected from alkenes having the formula:

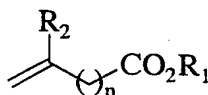


where R_3 = H or lower alkyl

5 R₄ = H or lower alkyl

m = 4 to 8

or



where R₁ = alkyl

10 R₂ = H or alkyl

n = 4 to 8.

11. A mixture obtainable by the process of any one of the preceding claims and containing at least one macrocyclic ketone in admixture with other incidental products of the process.

12. A mixture according to claim 11 wherein the macrocyclic ketone is muscone.

13. A perfume or perfumed product comprising a mixture according to claim 11 or 12.

14. A perfume according to claim 13 wherein the macrocyclic ketone is present in an amount of at least 0.01% by weight.

25 15. A perfumed product according to claim 13 wherein the macrocyclic ketone is present in an amount of at least 10 ppm by weight.

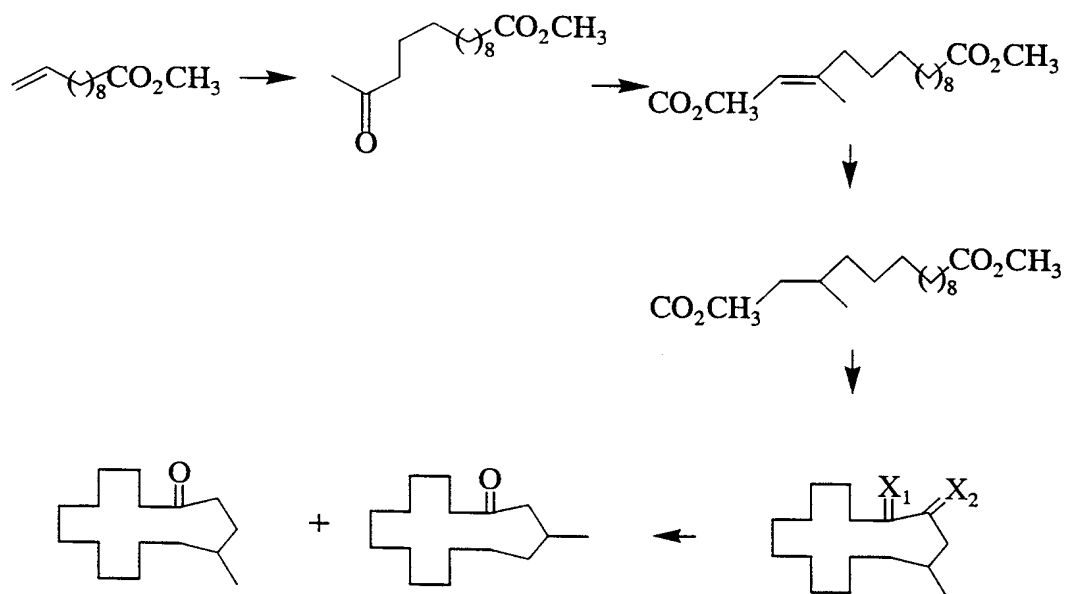


FIG 1

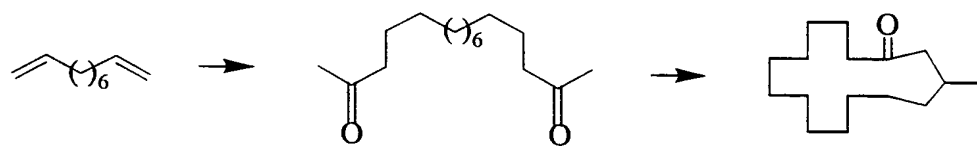


FIG 2